International Journal of Infectious Diseases (2009) **13**, 90—96

http://intl.elsevierhealth.com/journals/ijid

Fungemia in non-HIV-infected patients: a five-year review☆

Siriluck Anunnatsiri*, Ploenchan Chetchotisakd, Piroon Mootsikapun

Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, 40002, Thailand

Received 24 January 2008; received in revised form 10 April 2008; accepted 19 April 2008
Corresponding Editor: Sheldon Brown, New York, USA

KEYWORDS
Fungemia;
Candidemia;
Non-HIV;
Thailand

Summary
Objectives: To investigate the incidence, risk factors, causative fungi, and outcomes of fungemia in adult, non-HIV-infected patients.
Design: We studied 147 episodes of fungemia due to *Candida spp* and *Trichosporon spp* in adult patients admitted to a university hospital in Northeast Thailand between 1999 and 2003.
Results: The overall incidence of fungemia was 14.1 per 10 000 hospital admissions. Candida was the most common isolate (138 episodes, 93.9%) with non-albicans Candida accounting for 68.7%. The major non-albicans Candida isolates were *Candida parapsilosis* and *Candida tropicalis*. Fungemia caused by Trichosporon accounted for 6.1% of the cases, but their clinical features could not be distinguished from fungemia due to Candida. The overall in-hospital mortality rate was 56.1%. The independent factors related to mortality were high APACHE II score (odds ratio (OR) 1.12 per 1-point increments, 95% confidence interval (CI) 1.03—1.23), assisted ventilation (OR 3.49, 95% CI 1.04—11.64), and neutropenia (OR 7.47, 95% CI 1.25—44.74).
Conclusions: Candidemia, especially that caused by non-albicans Candida, was an important nosocomial infection in this tertiary care hospital in Northeast Thailand. The mortality rate was high, particularly in patients who were critically ill. Rapid diagnosis and early treatment are therefore important challenges for improving clinical outcomes.

Introduction

The incidence of nosocomial fungemia, most frequently as a result of *Candida spp* and on a some occasions as a result of *Trichosporon spp*, has dramatically increased in recent decades.[1] The increased incidence has been attributed to advances in modern medicine, e.g., organ transplantation, chemotherapeutic agents, invasive monitoring devices, parenteral nutrition, broad-spectrum antimicrobial agents, and assisted ventilation, all of which prolong survival but put patients at high risk of infection.

Fungemia has become a major cause of morbidity and mortality in hospitalized patients, and many studies have repeatedly identified the common independent risk factors

☆ This study was presented in part at the 13th International Congress on Infectious Diseases, Kuala Lumpur, Malaysia, 19—22 June, 2008 (final abstract number 45.005).

* Corresponding author. Tel.: +66 43 363664; fax: +66 43 348399.
E-mail address: asiril@kku.ac.th (S. Anunnatsiri).

1201-9712/$36.00
doi:10.1016/j.ijid.2008.04.009

including exposure to broad-spectrum antibiotics and chemotherapy, previous fungal colonization, indwelling catheterization, neutropenia, and hemodialysis.[1] However, several risk factors are still debated, such as corticosteroid treatment, underlying malignancy, parenteral nutrition, surgery, assisted ventilation, intensive care unit stay, and malnutrition.

The mortality rate among patients with fungemia has been found to be high, ranging between 50% and 80%.[1–5] Apart from the high mortality rate, there is concern that there has been a change in the epidemiology of candidemia, from *Candida albicans* infection to non-albicans Candida infection, specifically *Candida parapsilosis*, *Candida glabrata*, *Candida tropicalis*, and *Candida krusei*. Several studies have demonstrated the clinical importance of both *C. glabrata* and *C. krusei* as an emerging problem in association with the introduction of fluconazole prophylaxis.[6–9] High acute physiology and chronic health evaluation (APACHE) II scores, inadequate initial therapy, lack of antifungal therapy, and failure to remove central venous catheters were consistently identified as independent risk factors influencing mortality in fungemic patients, but the other factors (e.g., species of Candida, timing of initiation of antifungal treatment) remain unclear.[2,5,10]

In Thailand, the data related to fungemia are limited, therefore, we conducted a retrospective study to evaluate the incidence, risk factors, causative fungi, and outcomes of fungemia in adult, non-HIV-infected patients admitted to a tertiary care hospital in Northeast Thailand over five consecutive years.

Materials and methods

Between 1999 and 2003, all non-HIV-infected patients with fungemia, aged over 15 years, were identified through the records of the clinical microbiological laboratory at Srinagarind Hospital, a tertiary care, 760-bed, university hospital located in Northeast Thailand. The medical records of the identified patients were reviewed to recruit the study patients. Patients were included into the study if they had evidence of sepsis with at least one positive blood culture containing either Candida or Trichosporon.

Demographic data, the potential risk factors for developing fungemia presenting within 30 days prior to the diagnosis of fungemia, and outcomes were retrieved from the medical records. The following data were recorded: age, sex, type of infection (community-acquired vs. nosocomial infection following the definitions of the Centers for Diseases Control and Prevention), admission ward at onset of fungemia, comorbid diseases/conditions, duration of hospitalization before contracting fungemia, assisted ventilation, bacteremia, broad-spectrum antibiotic therapy, prior antifungal prophylaxis or treatment, fungal colonization, indwelling central venous catheterization or Foley's catheter, treatment with corticosteroid ($\geq$20 mg/day for $>$1 week), parenteral nutrition, surgical procedures, neutropenia (neutrophils $<0.5 \times 10^9$ cells/l), prolonged hospitalization ($>$30 days prior to the onset of candidemia), and stay in the intensive care unit (ICU). The severity of infection and concomitant bacteremia were also evaluated. Severity of illness was estimated using the APACHE II score on the day of positive blood culture or within 5 days of positive blood culture if the data were unavailable. Concomitant bacteremia was defined as the isolation of bacteria from the blood within 24 hours of the initial positive fungal culture.

Factors related to mortality in these patients, including age, presence of sepsis or septic shock, APACHE II score, steroid treatment, exposure to antimicrobial agents, parenteral nutrition, assisted ventilation, neutropenia, concomitant bacteremia, indwelling central venous catheterization, type of fungemia (primary vs. secondary fungemia), type of fungus (*C. albicans* vs. non-albicans Candida vs. other yeasts), and antifungal therapy were evaluated. The study protocol was approved by the Institutional Review Board of Khon Kaen University.

Blood cultures were processed using BacTAlert automated culture system following the manufacturer's instructions. Fungal isolates that formed chlamydospores were identified as *C. albicans*; further species identification was performed using sugar fermentation and assimilation characteristics based on standard methods.

Statistical analysis

Data analyses were performed using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA). To compare categorical variables, the Fisher's exact or Pearson's Chi-square tests were used as appropriate. The Wilcoxon and Kruskal–Wallis tests were used to test for statistical significance of the continuous variables as none of them were normally distributed. A p-value of <0.05 was considered statistically significant.

The parameters related to mortality were evaluated using a univariate analysis. All variables significantly associated with death on the univariate analysis were included in the multiple logistic regression analysis, using the backward likelihood ratio selection method. The results of the final model are presented as odds ratios (OR) with 95% confidence intervals (95% CIs).

Results

During the 5-year period, there were 147 episodes in 142 patients of positive blood culture for either Candida (138 episodes, 93.9%) or Trichosporon (nine episodes, 6.1%). Among the 138 Candida isolates, the most common was *C. parapsilosis* (40 episodes, 29.0%), followed by *C. albicans* and *C. tropicalis* (37 episodes each, 26.8%). *C. krusei*, *C. glabrata*, *Candida stellatoidea*, and *Candida rugosa* were isolated in two episodes each. The remaining 16 isolated blood cultures grew Candida, but species identification was not performed. The trend and distribution of fungi causing bloodstream infection are presented in Figure 1. The overall incidence of fungemia was 14.1 per 10 000 hospital admissions.

The medical records were available for 86 cases (58.5%). Of these, four cases were considered as contamination (two cases of Trichosporon isolates and one case each of *C. rugosa* and *Candida* species isolates) because of lack of clinical sepsis and presence of only one positive blood culture; these were then were excluded from the study. The demographic data of the remaining 82 patients are summarized in Table 1. The median age of these patients was 57 (range 16–85) years and approximately 2/3 were male. The majority of patients had underlying, predisposing diseases (75 cases, 91.5%): 21 cases (25.6%) of solid tumors, 15 (18.3%) of diabetes mellitus, 13 (15.9%) each of gastrointestinal/hepatobiliary diseases

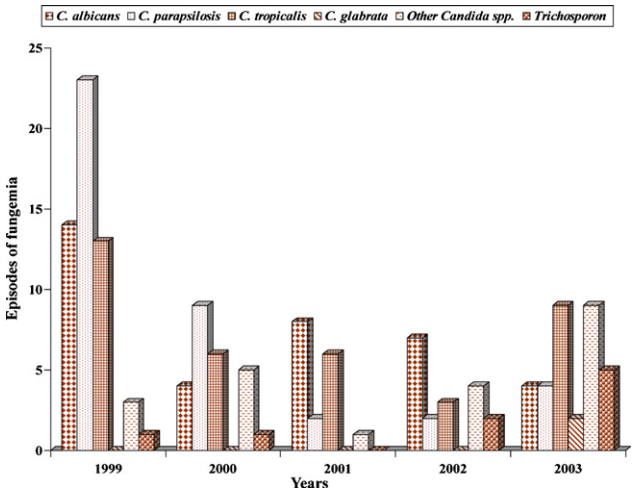

Figure 1 Trend and distribution of fungi causing bloodstream infection ($N = 147$).

and chronic kidney diseases, 11 (13.4%) of hematological cancer/diseases, and six (7.3%) of cardiovascular diseases. The median duration of hospitalization prior to contracting fungemia was 16.5 (range 0—163) days. The median APACHE II score was 19 (range 2—42).

All patients had at least one risk factor for developing fungemia, including indwelling Foley's catheter (53 cases, 64.6%), assisted ventilation (45 cases, 54.9%), central venous catheterization (44 cases, 53.7%), prior surgery (41 cases, 50%), prior ICU hospitalization (38 cases, 46.3%), fungal colonization (25 cases, 35.4%), prior abdominal surgery (28 cases, 34.1%), received parenteral nutrition (27 cases, 32.9%), received steroid treatment (20 cases, 24.4%), prolonged hospitalization (19 cases, 23.2%), received invasive procedure (15 cases, 18.3%), recent bacteremia (12 cases, 14.6%), and neutropenia (11 cases, 13.4%). All except two cases in patients with non-albicans candidemia had had prior antimicrobial therapy. The two most common classes of exposed antibiotic prior to developing fungemia were cephalosporins (56 cases, 70%) and aminoglycosides (37 cases, 46.3%).

Among the 82 cases, 54 (65.9%) and 23 (28.0%) patients had non-albicans candidemia and *C. albicans* candidemia, respectively. *C. tropicalis* (22 cases) and *C. parapsilosis* (21 cases) were the two most common isolates among those with non-albicans candidemia. The remaining five patients (6.1%) had fungemia from *Trichosporon* species. The demographic characteristics and risk factors for developing fungemia among these three groups of patients were not significantly different except for prior bacteremia ($p = 0.03$) and presence of fungal colonization ($p = 0.04$). Prior bacteremia and presence of fungal colonization were significantly more common in patients with *C. albicans* candidemia than those with non-albicans candidemia (7/23 cases (30.4%) vs. 4/54 cases (7.4%); $p = 0.01$, and 13/23 cases (56.5%) vs. 15/54 cases (27.8%); $p = 0.02$, respectively). Three cases in patients with non-albicans candidemia and one case in those with Trichosporon fungemia had received prior systemic anti-fungal therapy, but none of those with *C. albicans* candidemia had done so.

The overall in-hospital mortality rate was 56.1%. Fifty-one cases (62.2%) received systemic antifungal treatment with either amphotericin B deoxycholate or fluconazole. Of these, 11 cases (21.6%), 13 cases (25.5%), 6 cases (11.8%), and 21 cases (41.2%) started antifungal treatment within 24 hours, 24—48 hours, 48—72 hours, and >72 hours of positive blood culture, respectively. The mortality rate was not significantly different between patients who received antifungal treatment and those not treated (29/51 cases (56.9%) vs. 17/31 cases (54.8%); $p = 0.86$).

In the univariate analysis, the factors significantly associated with death were the presence of septic shock (OR 10.93, 95% CI 2.33—51.19), higher APACHE II score (OR 1.16 per 1-point increments, 95% CI 1.07—1.26), having received prednisolone ≥20 mg/day or other steroid with equivalent dose (OR 4.27, 95% CI 1.28—14.22), and assisted ventilation (OR 8.50, 95% CI 3.12—23.13) (Table 2).

In the multivariate analysis, three factors were related to mortality in the studied patients, including high APACHE II score (OR 1.12 per 1-point increments, 95% CI 1.03—1.23), assisted ventilation (OR 3.49, 95% CI 1.04—11.64), and neutropenia (OR 7.47, 95% CI 1.25—44.74).

Discussion

The incidence of nosocomial fungal infections has increased in recent years and this has raised concerns because it is associated with substantial mortality and medical costs.[1] The overall incidence of fungemia among non-HIV-infected, adult patients in our institution was also high and had a major impact on mortality, as 56% of patients died. The majority of nosocomial fungal infections (approximately 80%) are reportedly caused by *Candida spp*, and these organisms are the predominant fungi isolated from patient blood.

In our present study, Candida causing bloodstream infections accounted for 93.9% of fungemia. Non-albicans Candida causing fungemia, particularly *C. parapsilosis* and *C. tropicalis*, predominated. The uncommon, difficult-to-treat yeasts causing fungemia, Trichosporon, have raised concerns at our institution although they presented in only a small proportion (6.1%) of the cases, because their clinical features could not be distinguished from fungemia due to Candida.

Similarly, in another retrospective study conducted at a different university hospital in Thailand, Jutivorakool et al. found that the incidence of candidemia caused by non-albicans Candida (55.7%) tended to be higher than that for *C. albicans*. Data on the predominant species of non-albicans Candida in their study, however, were limited because species identification was performed on only 12.2% of non-albicans Candida.[11]

Between 1999 and 2000, the incidence of *C. parapsilosis* at our institution was remarkable; outbreak occurrence, the increase in use of central venous catheters, and parenteral nutrition were suspected. The retrospective nature of our study limits the investigation of these possibilities. Not having a fluconazole prophylaxis recommendation at our institution could be the reason why there has not been an emerging problem of *C. glabrata* or *C. krusei* as seen in many other institutions.[6,12,13]

Underlying and/or pre-existing diseases are commonly present in patients with fungemia; indeed, these affected up to three-quarters of the patients in our present study.

Table 1 Demographic data and risk factors for fungemia in the patients ($N = 82$)

Characteristics	Types of fungal isolation, *n* (%)				*p*-Value
	C. albicans 23 (28.0)	Non-*C. albicans* 54 (65.9)	*Trichosporon* 5 (6.1)	Overall 82 (100)	
Median age, years (range)	61 (21—85)	57 (16—77)	42 (19—52)	57 (16—85)	0.05
Male	15 (65.2)	33 (61.1)	1 (20.0)	49 (59.8)	0.16
Nosocomial infection	20 (87.0)	49 (90.7)	4 (80.0)	73 (89.0)	0.71
Admission ward at the onset of fungemia					0.68
Surgical ward	10 (43.5)	19 (35.2)	1 (20.0)	30 (36.6)	
Medical ward	6 (26.1)	19 (35.2)	3 (60.0)	28 (34.1)	
ICU	7 (30.4)	16 (29.6)	1 (20.0)	24 (29.3)	
Underlying diseases	22 (95.7)	48 (88.9)	5 (100.0)	75 (91.5)	0.49
Solid malignancy	6 (26.1)	14 (25.9)	1 (20.0)	21 (25.6)	0.96
Diabetes mellitus	4 (17.4)	11 (20.4)	0 (0.0)	15 (18.3)	0.53
Gastrointestinal/hepatobiliary diseases	6 (26.1)	6 (11.1)	1 (20.0)	13 (15.9)	0.25
Chronic kidney disease/stone	4 (17.4)	9 (16.7)	0 (0.0)	13 (15.9)	0.60
Hematologic malignancy/diseases	3 (13.0)	7 (13.0)	1 (20.0)	11 (13.4)	0.91
Cardiovascular diseases	3 (13.0)	3 (5.6)	0 (0.0)	6 (7.3)	0.42
Other	5 (21.7)	7 (13.0)	2 (40.0)	14 (17.1)	0.24
Associated risk factors					
Steroid treatment	6 (26.1)	12 (22.2)	2 (40.0)	20 (24.4)	0.66
Prior ICU hospitalization	14 (60.9)	22 (40.7)	2 (40.0)	38 (46.3)	0.26
Indwelling Foley's catheter	18 (78.3)	33 (61.1)	2 (40.0)	53 (64.6)	0.18
Central venous catheterization	15 (65.2)	28 (51.9)	1 (20.0)	44 (53.7)	0.17
Parenteral nutrition	7 (30.4)	17 (31.5)	3 (60.0)	27 (32.9)	0.41
Prior surgery	15 (65.2)	24 (44.4)	2 (40.0)	41 (50.0)	0.22
Prior abdominal surgery	7 (30.4)	20 (37.0)	1 (20.0)	28 (34.1)	0.68
Prolonged hospitalization	6 (26.1)	13 (24.1)	0 (0.0)	19 (23.2)	0.70
Prior bacteremia	7 (30.4)	4 (7.4)	1 (20.0)	12 (14.6)	0.03
Assisted ventilation	15 (65.2)	28 (51.9)	2 (40.0)	45 (54.9)	0.44
Fungal colonization	13 (56.5)	15 (27.8)	1 (20.0)	29 (35.4)	0.04
Neutropenia	1 (4.3)	9 (16.7)	1 (20.0)	11 (13.4)	0.36
Invasive procedure	7 (30.4)	8 (14.8)	0 (0.0)	15 (18.3)	0.15
Median APACHE score (range)	19.5 (8—38)	19 (2—42)	16 (3—21)	19 (2—42)	0.31
Median duration of hospitalization prior to fungemia, days (range)	19 (0—44)	15 (0—163)	18 (0—29)	16.5 (0—163)	0.77
Death	16 (69.6)	28 (51.9)	2 (40.0)	46 (56.1)	0.27

ICU, intensive care unit; APACHE, acute physiology and chronic health evaluation.

As found in several previous studies, solid-organ cancers, diabetes mellitus, gastrointestinal/hepatobiliary diseases, chronic kidney diseases, and hematological cancer/diseases were common underlying diseases.[1,6,14–16] The most common predisposing factors for contracting fungemia in our present study included the use of Foley's catheter or central venous catheter, receipt of steroid treatment or parenteral nutrition, use of broad-spectrum antibiotics, assisted ventilation, prior surgery or invasive procedure, prior ICU hospitalization, prior presence of fungal colonization, prolonged hospitalization, recent bacteremia, and neutropenia.

The importance of specific *Candida* species as an independent factor of death in candidemic patients has been the subject of controversy. Studies conducted by Alonso-Valle et al. and Weinberger et al., showed a negative impact of *C. albicans* on outcome compared to non-albicans Candida.[5,17] The crude mortality rate associated with *C. parapsilosis* infection has been lower than that reported for invasive infection with *C. albicans* or other non-albicans Candida.[18–20] *C. glabrata* candidemia may lead to an increased risk of mortality because of its lower susceptibility to antifungal agents; however Klevay et al. found that there was no difference in mortality rate between *C. albicans* and *C. glabrata* bloodstream infection.[21] In our study, we did not find either *C. albicans* or other non-albicans *Candida* species to be more associated with fatal outcome in these candidemic patients.

Several studies have demonstrated the importance of empirical antifungal therapy for patients suspected of having invasive candidemia, to improve survival and shorten hospitalization.[2,5,22–25] Lack of antifungal therapy has been demonstrated as an independent factor related to death in many studies; however this factor did not affect mortality in our study, which accords with results from the study conducted by Malani et al.[26] Failure to demonstrate the

Table 2 Factor associated with mortality in patients with fungemia by univariate and multivariate analysis

Variables	No. of deaths / No. of patients	Univariate analysis		Multivariate analysis	
		Crude OR	95% CI	Adjusted OR*	95% CI
Age, 1-point increments	46/82	1.00	0.97–1.02	-	-
APACHE II score, 1-point increments	46/82	1.16	1.07–1.26	1.12	1.03–1.23
Sepsis		1.29	0.08–21.29	-	-
Yes	45/80				
No	1/2				
Septic shock		10.93	2.33–51.19	-	-
Yes	18/20				
No	28/62				
Received steroid ≥20 mg/day					
Yes	16/20				
No	30/62	4.27	1.28–14.22	-	-
Received parenteral nutrition		0.99	0.39–2.56	-	-
Yes	14/25				
No	32/57				
Prior antimicrobial therapy		2.65	0.23–30.41	-	-
Yes	45/79				
No	1/3				
Assisted ventilation		8.50	3.12–23.13	3.49	1.04–11.64
Yes	34/43				
No	12/39				
Neutropenia		3.58	0.71–18.03	7.47	1.25–44.74
Yes	8/10				
No	38/72				
Concomitant bacteremia		1.05	0.22–5.01	-	-
Yes	4/7				
No	42/75				
Retained central venous catheter		3.06	0.68–13.79	-	-
Yes	14/18				
No	8/15				
Type of fungemia				-	-
Primary fungemia	32/53	1			
Secondary fungemia	14/29	0.61	0.25–1.53		
Type of fungus				-	-
C. albicans	16/23	1			
Non-*C. albicans*	28/54	0.45	0.16–1.28		
Other yeasts	2/5	0.44	0.05–3.76		
Time to starting antifungal therapy				-	-
Within 24 hours	8/11	1	0.11–3.40		
24–48 hours	8/13	0.60	0.05–3.00		
48–72 hours	3/6	0.38	0.07–1.65		
>72 hours	10/21	0.34			
Lack of antifungal therapy		0.92	0.38–2.26	-	-
Yes	17/31				
No	29/51				

* Factors adjusted in the multivariate analysis included APACHE (acute physiology and chronic health evaluation) II score, septic shock, assisted ventilation, received prednisolone >20 mg/day, type of fungus, and neutropenia.

beneficial effect of antifungal therapy may be explained by many confounders contributing to the cause of death in these patients or rapidly fatal illness in the course of infection.

As with several other studies, our present study shows that a high APACHE II score, assisted ventilation, and neutropenia are significantly associated with hospital mortality in these patients.[2,14,27] Patients with candidemia commonly had

co-morbidities and were critically ill. Prolonged neutropenia compromises the host defense mechanism against both bacterial and fungal infections. These factors are more likely to have the greatest impact for a grave prognosis among these patients.

Our study had several limitations. The major, very important limitation was the availability of medical records; these were available for only about half of the cases, and this could have caused a selection bias and distorted the outcomes of the study. Therefore, interpretation of the results should be done with extreme caution, and further well-defined studies are needed to confirm these outcomes. Secondly, we were unable to assess the reason for emergence of non-albicans candidemia in our setting. The retrospective nature of the study and the small sample size are major constraints. Finally, antifungal susceptibility was not performed in our institution so we could not evaluate whether the presence of antifungal resistance was an issue and might have affected mortality.

In summary, we have demonstrated the significance of candidemia as a cause of nosocomial infection and its significant impact on mortality at a tertiary care hospital in Northeast Thailand. Non-albicans Candida is a major contributor in our setting. Rapid diagnosis, reduction of severity in patients, and early empirical antifungal treatment in the high-risk groups are the challenges for improving clinical outcomes.

Acknowledgements

The authors thank the staff at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, for their care of the patients. Assistance from the Hospital Medical Chart Registration and Clinical Microbiological Laboratory staff is appreciated. We thank Mr Bryan Roderick Hamman for assistance with the English language presentation.

Conflict of interest: No conflict of interest to declare.

References

1. Fridkin SK, Jarvis WR. Epidemiology of nosocomial fungal infections. *Clin Microbiol Rev* 1996;**9**:499—511.
2. Viudes A, Pemán J, Cantón E, Ubeda P, López-Ribot JL, Gobernado M. Candidemia at a tertiary-care hospital: epidemiology, treatment, clinical outcome and risk factors for death. *Eur J Clin Microbiol Infect Dis* 2002;**21**:767—74.
3. Poikonen E, Lyytikäinen O, Anttila VJ, Ruutu P. Candidemia in Finland, 1995—1999. *Emerg Infect Dis* 2003;**9**:985—90.
4. Goldani LZ, Mário PS. *Candida tropicalis* fungemia in a tertiary care hospital. *J Infect* 2003;**46**:155—60.
5. Alonso-Valle H, Acha O, García-Palomo JD, Fariñas-Alvarez C, Fernández-Mazarrasa C, Fariñas MC. Candidemia in a tertiary care hospital: epidemiology and factors influencing mortality. *Eur J Clin Microbiol Infect Dis* 2003;**22**:254—7.
6. Abi-Said D, Anaissie E, Uzun O, Raad I, Pinzcowski H, Vartivarian S. The epidemiology of hematogenous candidiasis caused by different *Candida* species. *Clin Infect Dis* 1997;**24**:1122—8.
7. Pfaller MA, Diekema DJ, Jones RN, Sader HS, Fluit AC, Hollis RJ, et al. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and in vitro susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY Antimicrobial Surveillance Program. *J Clin Microbiol* 2001;**39**:3254—9.
8. Pfaller MA, Diekema DJ, Messer SA, Boyken L, Hollis RJ. Activities of fluconazole and voriconazole against 1586 recent clinical isolates of Candida species determined by broth microdilution, disk diffusion, and Etest methods: report from the ARTEMIS Global Antifungal Susceptibility Programm, 2001. *J Clin Microbiol* 2003;**41**:1440—6.
9. Messer SA, Jones RN, Fritsche TR. International surveillance of Candida spp and Aspergillus spp: report from the SENTRY Antimicrobial Surveillance Program (2003). *J Clin Microbiol* 2006;**44**:1782—7.
10. Fraser VJ, Jones M, Dunkel J, Storfer S, Medoff G, Dunagan WC. Candidemia in a tertiary care hospital: epidemiology, risk factors, and predictors of mortality. *Clin Infect Dis* 1992;**15**:414—21.
11. Jutivorakool K, Suankratay C, Tantawichien T, Chindamporn A. Candidemia in King Chulalongkorn Hospital: an eleven-year review (Abstract). The 29th Annual Meeting of the Infectious Disease Association of Thailand. Prajuabkirikan, Thailand, October 2003.
12. Wingard JR, Merz WG, Rinaldi MG, Johnson TR, Karp JE, Saral R. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. *N Engl J Med* 1991;**325**:1274—7.
13. Persons DA, Laughlin M, Tanner D, Perfect J, Gockerman JP, Hathorn JW. Fluconazole and *Candida krusei* fungemia. *N Engl J Med* 1991;**325**:1315.
14. Cheng YR, Lin LC, Young TG, Liu CE, Chen CH, Tsay RW. Risk factors for candidemia-related mortality at a medical center in central Taiwan. *J Microbiol Immunol Infect* 2006;**39**:155—61.
15. Costa SF, Marinho I, Araújo EA, Manrique AE, Medeiros EA, Levin AS. Nosocomial fungaemia: a 2-year prospective study. *J Hosp Infect* 2000;**45**:69—72.
16. Bassetti M, Trecarichi EM, Righi E, Sanguinetti M, Bisio F, Posteraro B, et al. Incidence, risk factors, and predictors of outcome of candidemia. Survey in 2 Italian university hospitals. *Diagn Microbiol Infect Dis* 2007;**58**:325—31.
17. Weinberger M, Leibovici L, Perez S, Samra Z, Ostfeld I, Levi I, et al. Characteristics of candidaemia with *Candida albicans* compared with non-albicans *Candida* species and predictors of mortality. *J Hosp Infect* 2005;**61**:146—54.
18. Nucci M, Colombo AL, Silveira F, Richtmann R, Solomao R, Branchini ML, et al. Risk factors for death in patients with candidaemia. *Infect Control Hosp Epidemiol* 1998;**19**:846—50.
19. Yamamura DL, Rotstein C, Nicolle LE, Loannou S. Candidaemia at selected Canadian sites: results from the Fungal Disease Registry, 1992—1994. Fungal Disease Registry of the Canadian Infectious Disease Society. *CMAJ* 1999;**160**:493—9.
20. Pappas PG, Rex JH, Lee J, Hamill RJ, Larsen RA, Powderly W, et al. A prospective observational study of candidaemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. *Clin Infect Dis* 2003;**37**:634—43.
21. Klevay MJ, Ernst EJ, Hollanbaugh JL, Miller JG, Pfaller MA, Diekema DJ. Therapy and outcome of *Candida glabrata* versus *Candida albicans* bloodstream infection. *Diagn Microbiol Infect Dis* 2007;**60**:273—7.
22. Nolla-Salas J, Sitges-Serra A, León-Gil C, Martínez-González J, León-Regidor MA, Ibáñez-Lucía P, et al. Candidemia in non-neutropenic critically ill patients: analysis of prognostic factors and assessment of systemic antifungal therapy. Study Group of Fungal Infection in the ICU. *Intensive Care Med* 1997;**23**:23—30.
23. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of Candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. *Antimicrob Agents Chemother* 2005;**49**:3640—5.

24. Macphail GL, Taylor GD, Buchanan-Chell M, Ross C, Wilson S, Kureishi A. Epidemiology, treatment and outcome of candidemia: a five-year review at three Canadian hospitals. *Mycoses* 2002;**45**:141—5.
25. Garey KW, Rege M, Pai MP, Mingo DE, Suda KJ, Turpin RS, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis* 2006;**43**:25—31.
26. Malani A, Hmoud J, Chiu L, Carver PL, Bielaczyc A, Kauffman CA. *Candida glabrata* fungemia: experience in a tertiary care center. *Clin Infect Dis* 2005;**41**:975—81.
27. Ben-Abraham R, Keller N, Teodorovitch N, Barzilai A, Harel R, Barzilay Z, et al. Predictors of adverse outcome from candidal infection in a tertiary care hospital. *J Infect* 2004; **49**:317—23.